Docket No.: PF-0356-4 CPA

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1652

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Lal et al.

Title: HUMAN REGULATORY MOLECULES

Serial No.: 09/840,787 Filing Date: April 23, 2001

Examiner: Slobodyansky, E. Group Art Unit 1652

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REPLY BRIEF

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated **October 20, 2003** ("the Examiner's Answer") in the above-identified application.

In the Examiner's Answer the Patent Examiner maintained the rejection under 35 U.S.C. §§ 101 and 112, first paragraph of claims 2-14 and 21 for alleged lack of utility.

The Examiner's Answer contains arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Lal '750 priority application relating to the use of the SEQ ID NO:19-encoding polynucleotides for gene expression monitoring applications. Such gene expression monitoring applications are highly useful in drug development and in toxicity testing.

The new positions and arguments in the Examiner's Answer include that (a) the Lal '750 application allegedly does not disclose toxicology testing (Examiner's Answer, e.g., pages 10-11); and (b) the gene expression monitoring results obtained using the claimed SEQ ID NO:19-encoding polynucleotides are allegedly not specific, not meaningful, or otherwise insufficient to constitute substantial, specific and credible utilities for the SEQ ID NO:19-encoding polynucleotides (Examiner's Answer, e.g., page 12). The Examiner's Answer further asserts that certain of the previously submitted references describing expression profiling were published after the filing date of the instant application and therefore allegedly do not "provide evidence that, as of the date the present application was filed, those of skill in the art would have recognized the asserted utilities as well-established" (Examiner's Answer, page 11).

Under the circumstances, Applicants are submitting with this Reply Brief :

The Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A-E;

The Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132; and

Nine (9) references published before the September 23, 1997 priority date of the instant application:

a. WO 95/21944, SmithKline Beecham, "Differentially expressed genes in healthy and diseased subjects" (Aug. 17, 1995)

b. WO 95/20681, Incyte Pharmaceuticals, "Comparative Gene Transcript Analysis" (Aug 3, 1995)

c. Schena et al., "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," Science 270:467-470 (Oct 20, 1995)

d. WO 95/35505, Stanford University, "Method and apparatus for fabricating microarrays of biological samples" (Dec 28, 1995)

e. U.S. Pat. No. 5,569,588, Ashby et al., "Methods for Drug Screening" (Oct 29, 1996)

f. Heller al., "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays," *PNAS* 94:2150 - 2155 (Mar 1997)

g. WO 97/13877, Lynx Therapeutics, "Measurement of Gene Expression Profiles in Toxicity Determinations" (April 17, 1997)

h. Acacia Biosciences Press Release (August 11, 1997)

i. Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Sept. 15, 1997)

As we will show, the Iyer Declaration, the Second Bedilion Declaration, and the accompanying references show the many substantial reasons why the Examiner's new positions and arguments with respect to the use of the claimed SEQ ID NO:19-encoding polynucleotides in gene expression monitoring applications are without merit.

The fact that the Iyer and Second Bedilion Declarations, along with the accompanying references, are being submitted in response to positions taken and arguments made for the first time in the Examiner's Answer, including arguments disregarding the persuasiveness of the first Bedilion Declaration, constitutes by itself "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations and references were not earlier submitted and should be admitted at this time. Appellants also note that the submitted Declarations and references are responsive to the new utility rejection as framed by the Board of Appeals in copending cases with similar issues.

I. UTILITY REJECTIONS

A. Overview of Utility Rejections

In the rejections of the claimed invention for alleged lack of utility, the Examiner's Answer does not disprove the following:

1) that the claimed polynucleotide encodes a mitochondrial carrier that is expressed in humans; and

2) that all, or almost all, mitochondrial carriers as well as polynucleotides expressed in humans have specific and substantial utility for measuring undesired side effects of drug candidates in toxicological testing.

It follows that the claimed invention is, by **more** than a reasonable probability, useful. There is no dispute that the Appellants need show no more than a reasonable probability that the claimed invention is useful to meet the requirements of 35 U.S.C. § 101 and § 112, first paragraph.

The Examiner's Answer never assails or even addresses this compelling logic. The Examiner's Answer continues to insist that the Appellants prove not only reasonable probability of utility, **but also** the biological or physical function of the claimed invention.

Nothing in the law requires Appellants to prove biological function, and the Examiner's Answer does not point to anything in the law suggesting such a requirement. Indeed, the only law on point is to the contrary: it is settled law -- and the Examiner's Answer does not rebut this -- that how an invention works (that is, its function) is utterly irrelevant to the utility analysis. In short, the entirety of the argument in the Examiner's Answer is based on the confusion between, and the improper equation of, use and function.

Application of the same logic to this case yields a completely different result. In this case, Appellants have identified the claimed polynucleotides by association in a defined and narrow group: genes that encode mitochondrial carriers, as well as expressed polynucleotides. As demonstrated below and in the Appeal Brief and First Bedilion Declaration, because mitochondrial carriers as well as expressed polynucleotides are predominantly useful, Appellants can state with great confidence that the claimed invention is useful. How the invention actually works is utterly irrelevant to the analysis.

B. The use of the claimed polynucleotides in expression profiling analyses were well-established prior to Appellants' filing date

The Examiner's Answer asserts that the utilities of the claimed polynucleotides in expression profiling and toxicology testing would allegedly not have been recognized by one of skill in the art as well-established at the time of filing (Examiner's Answer, page 11). Appellants submit two additional expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and nine (9) scientific references filed before the September 23, 1997 priority date of the instant application. The First Bedilion Declaration, Iyer Declaration, Second Bedilion Declaration, and the nine (9) references fully establish that, prior to the September 23, 1997 filing date of the priority Lal '750 application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to

survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;

with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

> it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;
>
> failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and
>
> failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

In his Declaration, Dr. Iyer explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe." (Iyer Declaration, ¶ 9.) In his second Declaration, Dr. Bedilion explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that "[i]t was ***never*** a question: our customers wanted ever more genes on the array, each new gene-specific probe providing incrementally more value to the customer" (Second Bedilion Declaration, ¶ 4).

Further evidence of the well-established utility of all expressed polypeptides and polynucleotides in toxicology testing is found in U.S. Pat. No. 5,569,588 (Reference No. 5) and published PCT applications WO 95/21944 (Reference No. 1), WO 95/20681 (Reference No. 2), and WO 97/13877 (Reference No. 7).

WO 95/21944 ("Differentially expressed genes in healthy and diseased subjects"), published August 17, 1995, describes the use of microarrays in expression profiling analyses, emphasizing that *patterns* of expression can be used to distinguish healthy tissues from diseased tissues and that *patterns* of expression can additionally be used in drug development and toxicology studies, without knowledge of the biological function of the encoded gene product. In particular, and with emphasis added:

> The present invention involves . . . methods for diagnosing diseases . . . characterized by the presence of [differentially expressed] . . . genes, despite the absence

of knowledge about the gene or its function. The methods involve the use of a composition suitable for use in hybridization which consists of a solid surface on which is immobilized at pre-defined regions thereon a plurality of defined oligonucleotide/ polynucleotide sequences for hybridization. Each sequence comprises a fragment of an EST. . . . Differences in hybridization patterns produced through use of this composition and the specified methods enable diagnosis of diseases based on differential expression of genes of unknown function . . . . [abstract]

The method [of the present invention] involves producing and comparing hybridization patterns formed between samples of expressed mRNA or cDNA polynucleotide sequences . . . and a defined set of oligonucleotide/polynucleotide[] . . . immobilized on a support. Those defined [immobilized] oligonucleotide/polynucleotide sequences are representative of the total expressed genetic component of the cells, tissues, organs or organism as defined by the collection of partial cDNA sequences (ESTs). [page 2]

The present invention meets the unfilled needs in the art by providing methods for the . . . use of gene fragments and genes, even those of unknown full length sequence and unknown function, which are differentially expressed in a healthy animal and in an animal having a specific disease or infection by use of ESTs derived from DNA libraries of healthy and/or diseased/infected animals. [page 4]

Yet another aspect of the invention is that it provides . . . a means for . . . monitoring the efficacy of disease treatment regimes including . . . toxicological effects thereof." [page 4]

It has been appreciated that one or more differentially identified EST or gene-specific oligonucleotide/polynucleotides define a pattern of differentially expressed genes diagnostic of a predisease, disease or infective state. A knowledge of the specific biological function of the EST is not required only that the EST[] identifies a gene or genes whose altered expression is associated reproducibly with the predisease, disease or infectious state. [page 4]

As used herein, the term 'disease' or 'disease state' refers to any condition which deviates from a normal or standardized healthy state in an organism of the same species in terms of differential expression of the organism's genes. . . [whether] of genetic or environmental origin, for example, an inherited disorder such as certain breast cancers. . . .[or] administration of a drug or exposure of the animal to another agent, e.g., nutrition, which affects gene expression. [page 5]

As used herein, the term 'solid support' refers to any known substrate which is useful for the immobilization of large numbers of oligonucleotide/polynucleotide

sequences by any available method . . . [and includes, inter alia,] nitrocellulose, . . . glass, silica. . . . [page 6]

By 'EST' or 'Expressed Sequence Tag' is meant a partial DNA or cDNA sequence of about 150 to 500, more preferably about 300, sequential nucleotides. . . . [page 6]

One or more libraries made from a single tissue type typically provide at least about 3000 different (i.e., unique) ESTs and potentially the full complement of all possible ESTs representing all cDNAs e.g., 50,000 – 100,000 in an animal such as a human. [page 7]

The lengths of the defined oligonucleotide/ polynucleotides may be readily increased or decreased as desired or needed. . . . The length is generally guided by the principle that it should be of sufficient length to insure that it is on[] average only represented once in the population to be examined. [page 7]

Comparing the . . . hybridization patterns permits detection of those defined oligonucleotide/ polynucleotides which are differentially expressed between the healthy control and the disease sample by the presence of differences in the hybridization patterns at pre-defined regions [of the solid support]. [page 13]

It should be appreciated that one does not have to be restricted in using ESTs from a particular tissue from which probe RNA or cDNA is obtained[;] rather any or all ESTs (known or unknown) may be placed on the support. Hybridization will be used [to] form diagnostic patterns or to identify which particular EST is detected. For example, all known ESTs from an organism are used to produce a 'master' solid support to which control sample and disease samples are alternately hybridized. [page 14]

Diagnosis is accomplished by comparing the two hybridization patterns, wherein substantial differences between the first and second hybridization patterns indicate the presence of the selected disease or infection in the animal being tested. Substantially similar first and second hybridization patterns indicate the absence of disease or infection. This[,] like many of the foregoing embodiments[,] may use known or unknown ESTs derived from many libraries. [page 18]

Still another intriguing use of this method is in the area of monitoring the effects of drugs on gene expression, both in laboratories and during clinical trials with animal[s], especially humans. [page 18]

WO 95/20681 ("Comparative Gene Transcript Analysis"), filed in 1994 by Appellants' assignee and published August 3, 1995, has three issued U.S. counterparts: U.S. Pat. Nos. 5,840,484,

issued November 24, 1998; 6,114,114, issued September 5, 2000; and 6,303,297, issued October 16, 2001.

The specification describes the use of transcript expression *patterns,* or "images", each comprising multiple pixels of gene-specific information, for diagnosis, for cellular phenotyping, and in toxicology and drug development efforts. The specification describes a plurality of methods for obtaining the requisite expression data -- one of which is microarray hybridization -- and equates the uses of the expression data from these disparate platforms. In particular, and with emphasis added:

> The invention provides a "method and system for quantifying the relative abundance of gene transcripts in a biological specimen. . . . [G]ene transcript imaging can be used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells. The invention provides a method for comparing the gene transcript image analysis from two or more different biological specimens in order to distinguish between the two specimens and identify one or more genes which are differentially expressed between the two specimens." [abstract]
>
> "[W]e see each individual gene product as a 'pixel' of information, which relates to the expression of that, and only that, gene. We teach herein [] methods whereby the individual 'pixels' of gene expression information can be combined into a single gene transcript 'image,' in which each of the individual genes can be visualized simultaneously and allowing relationships between the gene pixels to be easily visualized and understood." [page 2]
>
> "The present invention avoids the drawbacks of the prior art by providing a method to quantify the relative abundance of multiple gene transcripts in a given biological specimen. . . . The method of the instant invention provides for detailed diagnostic comparisons of cell profiles revealing numerous changes in the expression of individual transcripts." [page 6]
>
> "High resolution analysis of gene expression be used directly as a diagnostic profile. . . . " [page 7]
>
> "The method is particularly powerful when more than 100 and preferably more than 1,000 gene transcripts are analyzed." [page 7]
>
> "The invention . . . includes a method of comparing specimens containing gene transcripts." [page 7]
>
> "The final data values from the first specimen and the further identified sequence values from the second specimen are processed to generate ratios of transcript

sequences, which indicate the differences in the number of gene transcripts between the two specimens." [i.e., the results yield analogous data to microarrays] [page 8]

"Also disclosed is a method of producing a gene transcript image analysis by first obtaining a mixture of mRNA, from which cDNA copies are made." [page 8]

"In a further embodiment, the relative abundance of the gene transcripts in one cell type or tissue is compared with the relative abundance of gene transcript numbers in a second cell type or tissue in order to identify the differences and similarities." [page 9]

"In essence, the invention is a method and system for quantifying the relative abundance of gene transcripts in a biological specimen. The invention provides a method for comparing the gene transcript image from two or more different biological specimens in order to distinguish between the two specimens. . . . " [page 9]

"[T]wo or more gene transcript images can be compared and used to detect or diagnose a particular biological state, disease, or condition which is correlated to the relative abundance of gene transcripts in a given cell or population of cells." [pages 9-10]

"The present invention provides a method to compare the relative abundance of gene transcripts in different biological specimens. . . . This process is denoted herein as gene transcript imaging. The quantitative analysis of the relative abundance for a set of gene transcripts is denoted herein as 'gene transcript image analysis' or 'gene transcript frequency analysis'. The present invention allows one to obtain a profile for gene transcription in any given population of cells or tissue from any type of organism." [page 11]

"The invention has significant advantages in the fields of diagnostics, toxicology and pharmacology, to name a few." [page 12]

"[G]ene transcript sequence abundances are compared against reference database sequence abundances including normal data sets for diseased and healthy patients. The patient has the disease(s) with which the patient's data set most closely correlates." [page 12]

"For example, gene transcript frequency analysis can be used to differentiate normal cells or tissues from diseased cells or tissues. . . ." [page 12]

"In toxicology, . . . [g]ene transcript imaging provides highly detailed information on the cell and tissue environment, some of which would not be obvious in conventional, less detailed screening methods. The gene transcript image is a more powerful method to predict drug toxicity and efficacy. Similar benefits accrue in the use of this tool in pharmacology. . . . " [page 12]

"In an alternative embodiment, comparative gene transcript frequency analysis is used to differentiate between cancer cells which respond to anti-cancer agents and those which do not respond." [page 12]

"In a further embodiment, comparative gene transcript frequency analysis is used . . . for the selection of better pharmacologic animal models." [page 14]

"In a further embodiment, comparative gene transcript frequency analysis is used in a clinical setting to give a highly detailed gene transcript profile of a diseased state or condition." [page 14]

"An alternate method of producing a gene transcript image includes the steps of obtaining a mixture of test mRNA and providing a representative array of unique probes whose sequences are complementary to at least some of the test mRNAs. Next, a fixed amount of the test mRNA is added to the arrayed probes. The test mRNA is incubated with the probes for a sufficient time to allow hybrids of the test mRNA and probes to form. The mRNA-probe hybrids are detected and the quantity determined." [page 15]

"[T]his research tool provides a way to get new drugs to the public faster and more economically." [page 36]

"In this method, the particular physiologic function of the protein transcript need not be determined to qualify the gene transcript as a clinical marker." [page 38]

"[T]he gene transcript changes noted in the earlier rat toxicity study are carefully evaluated as clinical markers in the followed patients. Changes in the gene transcript image analyses are evaluated as indicators of toxicity by correlation with clinical signs and symptoms and other laboratory results. . . . The . . . analysis highlights any toxicological changes in the treated patients." [page 39]

U.S. Pat. No. 5,569,588 ("Methods for Drug Screening") ("the '588 patent"), issued October 29, 1996, with a priority date of August 1995, describes an expression profiling platform, the "genome reporter matrix", which is different from nucleic acid microarrays. Additionally describing use of nucleic acid microarrays, the '588 patent makes clear that the utility of comparing multidimensional expression datasets is independent of the methods by which such profiles are obtained. The '588 patent speaks clearly to the usefulness of such expression analyses in drug development and toxicology, particularly pointing out that a gene's failure to change in expression level is a useful result. Thus, with emphasis added,

The invention provides "[m]ethods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug. . . . [The final step of the method comprises] comparing reporter gene product signals for each cell before and after contacting the cell with the candidate drug to obtain a drug response profile which provides a model of the transcriptional responsiveness of said organism to the candidate drug." [abstract]

"The present invention exploits the recent advances in genome science to provide for the rapid screening of large numbers of compounds against a systemic target comprising substantially all targets in a pathway [or] organism." [col. 1]

"The ensemble of reporting cells comprises as comprehensive a collection of transcription regulatory genetic elements as is conveniently available for the targeted organism so as to most accurately model the systemic transcriptional response. Suitable ensembles generally comprise thousands of individually reporting elements; preferred ensembles are substantially comprehensive, i.e. provide a transcriptional response diversity comparable to that of the target organism. Generally, a substantially comprehensive ensemble requires transcription regulatory genetic elements from at least a majority of the organism's genes, and preferably includes those of all or nearly all of the genes. We term such a substantially comprehensive ensemble a genome reporter matrix." [col. 2]

"Drugs often have side effects that are in part due to the lack of target specificity. . . . [A] genome reporter matrix reveals the spectrum of other genes in the genome also affected by the compound. In considering two different compounds both of which induce the ERG10 reporter, if one compound affects the expression of 5 other reporters and a second compound affects the expression of 50 other reports, the first compound is, a priori, more likely to have fewer side effects." [cols. 2 - 3]

"Furthermore, it is not necessary to know the identity of any of the responding genes." [col. 3]

"[A]ny new compound that induces the same response profile as [a] . . . dominant tubulin mutant would provide a candidate for a taxol-like pharmaceutical." [col. 4]

"The genome reporter matrix offers a simple solution to recognizing new specificities in combinatorial libraries. Specifically, pools of new compounds are tested as mixtures across the matrix. If the pool has any new activity not present in the original lead compound, new genes are affected among the reporters." [col. 4]

" A sufficient number of different recombinant cells are included to provide an ensemble of transcriptional regulatory elements of said organism sufficient to model the

transcriptional responsiveness of said organism to a drug. In a preferred embodiment, the matrix is substantially comprehensive for the selected regulatory elements, e.g. essentially all of the gene promoters of the targeted organism are included." [cols. 6-7]

"In a preferred embodiment, the basal response profiles are determined. . . . The resultant electrical output signals are stored in a computer memory as genome reporter output signal matrix data structure associating each output signal with the coordinates of the corresponding microtiter plate well and the stimulus or drug. This information is indexed against the matrix to form reference response profiles that are used to determine the response of each reporter to any milieu in which a stimulus may be provided. After establishing a basal response profile for the matrix, each cell is contacted with a candidate drug. The term drug is used loosely to refer to agents which can provoke a specific cellular response. . . . The drug induces a complex response pattern of repression, silence and induction across the matrix . . . .The response profile reflects the cell's transcriptional adjustments to maintain homeostasis in the presence of the drug. . . . After contacting the cells with the candidate drug, the reporter gene product signals from each of said cells is again measured to determine a stimulated response profile. The basal o[r] background response profile is then compared with . . . the stimulated response profile to identify the cellular response profile to the candidate drug." [cols. 7-8]

"In another embodiment of the invention, a matrix [i.e., array] of hybridization probes corresponding to a predetermined population of genes of the selected organism is used to specifically detect changes in gene transcription which result from exposing the selected organism or cells thereof to a candidate drug. In this embodiment, one or more cells derived from the organism is exposed to the candidate drug in vivo or ex vivo under conditions wherein the drug effects a change in gene transcription in the cell to maintain homeostasis. Thereafter, the gene transcripts, primarily mRNA, of the cell or cells is isolated . . . [and] then contacted with an ordered matrix [array] of hybridization probes, each probe being specific for a different one of the transcripts, under conditions where each of the transcripts hybridizes with a corresponding one of the probes to form hybridization pairs. The ordered matrix of probes provides, in aggregate, complements for an ensemble of genes of the organism sufficient to model the transcriptional responsiveness of the organism to a drug. . . . The matrix-wide signal profile of the drug-stimulated cells is then compared with a matrix-wide signal profile of negative control cells to obtain a specific drug response profile." [col. 8]

"The invention also provides means for computer-based qualitative analysis of candidate drugs and unknown compounds. A wide variety of reference response profiles may be generated and used in such analyses." [col. 8]

"Response profiles for an unknown stimulus (e.g. new chemicals, unknown compounds or unknown mixtures) may be analyzed by comparing the new stimulus response profiles with response profiles to known chemical stimuli." [col. 9]

"The response profile of a new chemical stimulus may also be compared to a known genetic response profile for target gene(s)." [col. 9]

The August 11, 1997 press release from the '588 patent's assignee, Acacia Biosciences (now part of Merck) (reference "h" attached hereto), and the September 15, 1997 news report by Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," *Genetic Engineering News* (reference "i" attached hereto), attest the commercial value of the methods and technology described and claimed in the '588 patent.

WO 97/13877 ("Measurement of Gene Expression Profiles in Toxicity Determinations"), published April 17, 1997, describes an expression profiling technology differing somewhat from the use of cDNA microarrays and differing from the genome reporter matrix of the '588 patent; but the use of the data is analogous. As per its title, the reference describes use of expression profiling in toxicity determinations. In particular, and with emphasis added:

"[T]he invention relates to a method for detecting and monitoring changes in gene expression patterns in in vitro and in vivo systems for determining the toxicity of drug candidates." [Field of the invention]

"An object of the invention is to provide a new approach to toxicity assessment based on an examination of gene expression patterns, or profiles, in in vitro or in vivo test systems." [page 3]

"Another object of the invention is to provide a rapid and reliable method for correlating gene expression with short term and long term toxicity in test animals." [page 3]

"The invention achieves these and other objects by providing a method for massively parallel signature sequencing of genes expressed in one or more selected tissues of an organism exposed to a test compound. An important feature of the invention is the application of novel . . . methodologies that permit the formation of gene expression profiles for selected tissues . . . . Such profiles may be compared with those from tissues of control organisms at single or multiple time points to identify expression patterns predictive of toxicity." [page 3]

"As used herein, the terms 'gene expression profile,' and 'gene expression pattern' which is used equivalently, means a frequency distribution of sequences of portions of cDNA molecules sampled from a population of tag-cDNA conjugates. . .. Preferably, the total number of sequences determined is at least 1000; more preferably, the total number of sequences determined in a gene expression profile is at least ten thousand." [page 7]

"The invention provides a method for determining the toxicity of a compound by analyzing changes in the gene expression profiles in selected tissues of test organisms exposed to the compound. . . . . Gene expression profiles derived from test organisms are compared to gene expression profiles derived from control organisms. . . . " [page 7]

C. Responses to Specific Arguments by Examiner

1. Disclosure of toxicology testing in the specification as filed

The Examiner's Answer asserts that "the specification nowhere mentions toxicology testing, and drug discovery" (Examiner's Answer, page 10), and that the only disclosure regarding microarrays "is applied in general to polynucleotides encoding any HRM not specifically to HRM-19" (Examiner's Answer, page 10). The fact that the specification discloses that the HRM proteins in general can be used in microarrays does not mean that the specific HRM-19 protein cannot also be so used. The Examiner's Answer further asserts that the specification does not disclose the use of microarrays for toxicology testing (Examiner's Answer, page 11). In fact, the section of the specification quoted in the Examiner's Answer states that microarrays comprising HRM-19 encoding sequences may be used "in developing and in monitoring the activities of therapeutic agents" (Lal '750 application, page 49, line 19). As stated in the First Bedilion Declaration:

. . . those of skill in the art who were working on drug development in September 1997 (and for many years prior to September 1997) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs . . . Accordingly, the teachings in the Lal '750 application, in particular regarding use of the SEQ ID NO:19-encoding polynucleotides in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly

includes toxicity studies and persons skilled in the art who read the Lal '750 application on September 23, 1997 would have understood that to be so. (First Bedilion Declaration, ¶ 10).

Thus one of skill in the, art, understanding that toxicology testing is one of the most important steps in drug development, would have understood the Lal '750 application's disclosure of drug development to include toxicology testing.

2. Toxicology testing is a specific utility

The Examiner's Answer asserts that "the asserted utility of the claimed polynucleotides - as a component of a microarray for monitoring gene expression - does not provide a specific benefit in currently available form" (Examiner's Answer, page 12).

Appellants' submission of additional facts overcomes this concern. Those facts demonstrate that, far from applying ***regardless*** of the specific properties of the claimed invention, the utility of Appellants' claimed polynucleotides as gene-specific probes ***depends upon*** specific properties of the polynucleotides, that is, their nucleic acid sequences.

"Each gene included as a probe on a microarray provides ***a signal that is specific to the cognate transcript***, at least to a first approximation."[1] Accordingly, "[e]ach new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device."[2]

Although not required for present purposes, it would be appropriate to state on the record here that the specificity of nucleic acid hybridization was well-established far earlier than the development of high density spotted microarrays in 1995, and indeed is the well-established underpinning of many, perhaps most, molecular biological techniques developed over the past 30 - 40 years.

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[1] Declaration of Dr. Vishwanath R. Iyer, ¶ 7 (emphasis added). See the footnote at ¶ 7 for a slightly more "nuanced" view.

[2] Declaration of Dr. Vishwanath R. Iyer, ¶ 7.

3. One of skill in the art would understand how to interpret the results of microarray-based experiments using the claimed polynucleotides

The Examiner's Answer asserts that the specification "does not disclose how to use the HRM-19-specific gene expression data generated by a microarray" (Examiner's Answer, page 13). Appellants respectfully point out that what is being measured in this case is not the expression level of the claimed polynucleotides as such, but the potential toxic effect of a therapeutic compound. The expression levels of the claimed polynucleotides are used as a **tool** to study the effect of the compound, not for the sake of performing further research on the invention itself.

The Examiner asks, if a researcher observed that HRM-19 expression was increased when a cell was treated with a particular agent, how would a skilled worker be able to determine "whether that result is meaningful" (Examiner's Answer, page 12). Dr. Bedilion in his First Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets" (First Bedilion Declaration ¶ 10 at page 8). Thus, if the expression of a particular polynucleotide is affected in any way by exposure to a test compound, and if that particular polynucleotide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polynucleotide sequence.

The Examiner' Answer is completely wrong to characterize Appellants' argument regarding utility as a control as somehow requiring the person using the invention to do further research to identify biological function (Examiner's Answer, page 13). The point is not whether or not the claimed polynucleotides are, in any given toxicology test, differentially expressed. The point is that the invention provides a useful measuring stick regardless of whether there is or is not differential expression. That makes the invention useful today, in the real-world, for real purposes having nothing to do with further characterization of the invention itself.

4. The claimed polynucleotides add utility to any microarray

The Examiner's Answer asserts that "the addition of a DNA encoding SEQ ID NO:19 to a microarray does not impart the utility if the microarray did not have one" (Examiner's Answer, page 14).

To the contrary, as discussed above in Section I..B., the currently submitted Declarations and references demonstrate that every new gene adds value to any microarray, because it increases the resolving power of the expression patterns generated by the microarray. As stated in the Iyer Declaration: "Each new gene-specific probe added to a microarray thus increases the number of genes detectable by the device, increasing the resolving power of the device. As I note above, higher resolution patterns are generally more useful in comparisons than lower resolution patterns. Accordingly, each new gene probe added to a microarray increases the usefulness of the device in gene expression profiling analyses" (Iyer Declaration, ¶ 7). The additional resolving power added by the HRM-19 encoding polynucleotides has practical, real-world uses in, for example, drawing finer distinctions between classes of cancers, permitting better customization of therapy (Iyer Declaration, ¶ 8).

5. The claimed sequences are a multipurpose research tool

The Examiner's Answer asserts that the specification does not disclose "what drug(s) HRM-19 would be useful in developing, or what specific disease(s) it would be useful in diagnosing (Examiner's Answer, page 10). In response to Appellants' previous explanations that the claimed polynucleotides can be used to develop drugs targeted to other genes or proteins, the Examiner's Answer asserts that the specification has not taught any other genes or proteins (Examiner's Answer, pages 16-17).

The Examiner appears to be missing the point. The claimed polynucleotides are useful in developing drugs targeted to many different genes and proteins, not just to specified targets. Just as a scale can be used to measure many different objects, or a ligase can be used to cleave many different DNAs, so too can the claimed polynucleotides be used to assess toxicity of many different drugs. The claimed sequences, and the arrays of which they may be a part, are a multipurpose tool. This tool can

be used, for example, to study primary and secondary drug effects, to discriminate and classify human cancers, and to elucidate basis physiological responses (Iyer Declaration, ¶¶ 3-4).

6. The legal standard for utility

The Examiner's Answer asserts that "[a]lthough each gene in the microarray contributes to the data generated by the microarray overall, the contribution of a single gene - its data point- is only a tiny contribution to the overall picture," and that "[a] patentable utility divided by a thousand does not necessarily equal a thousand patentable utilities" (Examiner's Answer, page 16).

The Court of Appeals for the Federal Circuit has made clear that even were the Examiner's conclusion that measurement of the level of expression of the claimed polynucleotide provides only a "tiny contribution" to such a picture correct, even such a pixel would assuredly suffice under 35 U.S.C. §101.

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result") [emphasis added]; *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984), quoted in *Stifftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991).

7. Biological function is irrelevant to utility

The Examiner's Answer asserts that HRM-19 is not asserted to be a mitochondrial carrier protein (Examiner's Answer, page 17). In fact, as the Examiner describes, HRM-19 is identified as being homologous to a *C. elegans* carrier protein, and as having a mitochondrial motif. Hence, the

obvious conclusion is that HRM-19 was identified as a protein having both these characteristics, that is, a mitochondrial carrier protein.

The Examiner's Answer further asserts that membership in the mitochondrial carrier family of proteins is not sufficient to impart utility to polynucleotides encoding HRM-19, because "mitochondrial carriers have widely varying activities" (Examiner's Answer, page 18). The Examiner is confusing, once again, function with use. These are not synonymous. Despite having different biological functions, mitochondrial carriers can indeed have many common uses, such as toxicology controls. In any event, it does not matter that there may be more than one use for mitochondrial carriers. The point for the purposes of the utility standard is that they are all indeed useful, which proves more than probable utility of the claimed invention.

8. Irrelevance of disease association and differential expression to utility in toxicology testing

The Examiner asserts that a DNA encoding HRM-19 would have utility if it were known to be differentially expressed in particular tissues or diseases (Examiner's Answer, page 14) or if it were disclosed to be associated with a specific disease (Examiner's Answer, page 15). This is irrelevant. Appellants need not demonstrate whether the claimed polynucleotides or the proteins they encode are associated with disease or differentially expressed, only whether the claimed polynucleotides are useful. The claimed polynucleotides are useful whether or not the claimed polynucleotides are associated with disease or differentially expressed (for example, as controls in toxicology testing for drugs directed to other genes or proteins).

While expressly not conceding that an association with specific diseases is necessary to demonstrate the utility of polynucleotides encoding HRM-19, Appellants respectfully point out the ample evidence indicating an association between HRM-19 and cell proliferative disorders. This includes, as previously discussed, the Lal Declaration submitted with the Response to Office Action filed September 3, 2002. The Lal Declaration demonstrates that polynucleotides encoding HRM-19 are overexpressed in lung tumor tissue as compared to normal lung tissue, and thus are useful in the diagnosis of lung cancer. In addition, the specification states that polynucleotides encoding HRM may

be used for the diagnosis of cancers, including cancers of the lung (Lal '750 application, page 47, lines 24-28). The use of polynucleotides encoding HRM to detect cancer, and the association of increased amounts of transcript with cancer is further disclosed in the specification at, for example, page 48, lines 7-16, and page 48, line 29 through page 49, line 1.

The Examiner's Answer asserts that the specification "provides no specific teaching regarding HRM-19 but only the teaching regarding all HRM in general" (Examiner's Answer, page 19). The fact that all of the disclosed HRMs have utility in the diagnosis of cancer does not mean that HRM-19 lacks this utility -- the disclosed utility naturally applies to HRM-19 as one member selected from the group of disclosed HRMs, as well as to the HRMs as a group. Furthermore, the Examiner's Answer ignores the disclosure specific to HRM-19 at, for example, page 18, lines 27-28, wherein the specification discloses that sequences encoding HRM-19 are found in cDNA libraries associated with cell proliferation and cancer.

D. The Examiner's Answer is Based on Flawed Assumptions about the Legal Standard for Utility

In the face of Appellants' demonstration of numerous disclosed and well-established utilities for the claimed polynucleotides, the Examiner's Answer does not offer any facts or sound scientific reasoning as would be required to overcome the presumption of utility that must be attributed to the claimed invention as a matter of law. For example, the Examiner's Answer has no answer for the disclosed utilities of the claimed polynucleotides in gene expression monitoring applications that are discussed under Section II of the Appeal Brief.

The Examiner's Answer has not and cannot provide **any** evidence tending to show that a person of ordinary skill in the art could not achieve the disclosed utilities, or indeed that any experimentation whatsoever would be required to put the claimed invention to beneficial use. And the Examiner's Answer utterly fails to address the Appellants' overwhelming evidence demonstrating not only that persons of ordinary skill in the art recognize the utility of inventions such as those claimed, but also that the likelihood that the claimed invention would achieve those utilities is far beyond substantial.

Apart from ignoring the presumption of utility and the Examiner's burden to overcome it, the entirety of the Examiner's Answer ultimately is based on three flawed assumptions. They are:

i. the claimed invention cannot be proven to be useful until the biological roles or functions of the proteins encoded by the claimed polynucleotides also are proven;

ii. assignment to a family whose members are known to be useful does not establish utility unless the members share a single, common utility; and,

iii. the *Brenner* v. *Manson* case somehow supports the Examiner's position in the present situation (Examiner's Answer, pages 13, 21).

All of these assumptions are incorrect.[3]

1. <u>The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility</u>

Rather than responding to Appellants' evidence demonstrating utility, the Examiner's Answer attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not specific, substantial, and credible utilities (Examiner's Answer at, for example, pages 14-16). The Examiner's Answer is incorrect both as a matter of law and as a matter of fact.

The basis of the argument in the Examiner's Answer is that, without information as to the precise biological role of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner's Answer, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed polynucleotides either individually or in a DNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner's Answer would require, in addition, that the applicant provide detailed interpretations of the results generated in any given expression analysis (Examiner's Answer, page 13).

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[3] It is respectfully submitted that the entirety of the Examiner's alleged rebuttal of Appellants' arguments and reasoning in the Examiner's Answer are based on these three incorrect assumptions. Nevertheless, to the extent that Appellants do not specifically rebut these points on a line-by-line basis, this is not to be construed as acquiescence to their veracity, and Appellants do not waive the right to rebut them individually at any later point in the proceedings.

It may be that such interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner's Answer would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999)[4]. If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt that the present invention easily meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

Biological role or function is, instead, merely one factor that can be relevant in demonstrating whether there is a "substantial likelihood" a claimed invention can achieve the identified benefits. It may be particularly helpful in those cases where it is necessary to prove that the identifiable benefit of one

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[4] *Juicy Whip* states:
An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

biological composition can be imputed to another. In these cases, see, *e.g.*, *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995), because there is no direct evidence that the biological composition can achieve any given utility, knowledge of biological function can be used to prove a "substantial likelihood" of utility indirectly, by association. Biological function serves as a link between a compound whose utility otherwise would be unknown and another compound having known utility. If, for example, a prior art biological composition is known to be a target in the treatment of disease, one way the applicant can prove utility is by demonstrating that the claimed invention is substantially likely to share the utility for disease treatment because it also shares a biological role with the prior art composition.

But in other cases, such as this one, proof of biological function is not necessary. In those cases, the evidence already is sufficient to show that there is a substantial likelihood that the claimed invention produces the alleged benefit. The claimed invention has a known utility whether or not it can be linked (through biological function) with some other composition.

By implicitly requiring knowledge of biological function for any claimed nucleic acid or protein, the Examiner's Answer has, contrary to law, elevated what has long been acknowledged to be an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

2. Assignment to a family whose members are useful establishes utility

For the reasons discussed in Section III.B of the Appeal Brief, the Examiner cannot properly impose a "common utility" requirement with respect to the mitochondrial carrier family and the family of expressed polynucleotides to which the sequences encoding HRM-19 belong. The Examiner's attempt to do so, if permitted to succeed, would improperly raise the threshold of patentable utility for biotechnological inventions to a point above that of other classes of inventions.

3. The Examiner's reliance on *Brenner* v. *Manson* is misplaced

This is not a case in which biological function is necessary to provide a link between the claimed invention on one hand, and a compound of known utility on the other. Given that the claimed invention is disclosed in the instant specification to be useful as a tool in a number of gene expression monitoring applications that were well-known at the time of the filing of the application in connection with the development of drugs and the monitoring of the activity of drugs, the precise biological function of the claimed polynucleotides or the proteins they encode is superfluous information for the purposes of establishing utility.

The uncontested fact that the claimed invention already has a disclosed use as a tool in then available technology (such as DNA microarrays) distinguishes it from those few claimed inventions found not to have utility. In each of those cases, unlike this one, the person of ordinary skill in the art was left to guess whether the claimed invention could be used to produce an identifiable benefit. Thus the Examiner's unsupported statement that one of those cases, *Brenner* v. *Manson*, 383 U.S. 519, 532, 534-35 (1966), is somehow analogous to this case is plainly incorrect.

Brenner concerns a narrow exception to the general rule that inventions are useful. It holds that where the assertion of utility for the claimed invention is made by association with a group including useful members, the group may not include so many useless members that there would be less than a substantial likelihood that the claimed invention is in fact one of the useful members of the group. In *Brenner*, the claimed invention was a process for making a synthetic steroid. Some steroids are useful, but most are not. While the claimed process in *Brenner* produced a composition that bore homology to some useful steroids, antitumor agents, it also bore structural homology to a substantial number of steroids having no utility at all. There was no evidence that could show, by substantial likelihood, that the claimed invention would produce the benefits of the small subset of useful steroids. It was entirely possible, and indeed likely, that the claimed invention was just as useless as the majority of steroids.

In *Brenner*, the steroid was not disclosed in the application for a patent to be useful in its then-present form. Here, in contrast, the claimed polynucleotide is an expressed polynucleotide that was disclosed to be useful in the instant specification for many known applications involving gene expression analysis. Its utility is not a matter of guesswork. It is not a random DNA sequence that might or might

not be useful as a scientific tool. Unlike the steroid in *Brenner*, the utility of the invention claimed here is not grounded upon being structurally analogous to a molecule which belongs to a class of molecules containing a significant number of useless compositions.[5]

And, the utilities disclosed in the application are for purposes other than just studying the claimed invention itself, *Brenner*, 383 U.S. at 535, i.e., for other (non self-referential) uses such as to ascertain the toxic potential of a drug candidate and to study the efficacy of a proposed drug for cell proliferative disorders.

Accordingly, in this case, biological function is in fact superfluous information for the purposes of demonstrating utility. Here, the claimed invention is more than "substantially likely" to be useful, in a way that is utterly independent of knowledge of precise biological function. Given that the claimed invention has disclosed and well-established utilities, the Appellants need not demonstrate utility by imputation.

In the end, the Examiner's Answer has failed to recognize that new technologies, such as those involving the use of DNA microarrays, to conduct gene expression analyses have made useful biological molecules that might not otherwise have been useful in the past. *See Brenner*, 383 U.S. at 536. Technology has now advanced well beyond the point that a person of ordinary skill in the art would have to guess whether a newly discovered expressed polynucleotide could be usefully employed without further research. It has created a need for new tools, such as the claimed polynucleotides, that provide, and have been providing for some time now, unquestioned commercial and scientific benefits, and **real-world benefits** to the public by enabling faster, cheaper and safer drug discovery processes. The Examiner is obliged, by law, to recognize this reality.

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[5] While not necessary to reverse the Examiner's rejections, it is appropriate to point out that because the SEQ ID NO:68 polynucleotide is an expressed human polynucleotide, it is highly more likely than not that it belongs to the class of molecules that have been pre-selected by nature to be useful.

II. ENABLEMENT REJECTIONS

The rejection set forth in the Examiner's Answer is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Examiner's Answer, page 9). To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

III. CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,
INCYTE CORPORATION

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Attached:
1. Second Declaration of Tod Bedilion, Ph.D., under 37 C.F.R. § 1.132;
2. Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E
3. Nine (9) references published before the filing date of the instant application:
a) WO 95/21944, SmithKline Beecham, "Differentially expressed genes in healthy and diseased subjects" (Aug. 17, 1995)
b) WO 95/20681, Incyte Pharmaceuticals, "Comparative Gene Transcript Analysis" (Aug 3, 1995)
c) Schena et al., "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," Science 270:467-470 (Oct 20, 1995)
d) WO 95/35505, Stanford University, "Method and apparatus for fabricating microarrays of biological samples" (Dec 28, 1995)
e) U.S. Pat. No. 5,569,588, Ashby et al., "Methods for Drug Screening" (Oct 29, 1996)
f) Heller al., "Discovery and analysis of inflammatory disease-related genes using cDNA microarrays," *PNAS* 94:2150 - 2155 (Mar 1997)

g) WO 97/13877, Lynx Therapeutics, "Measurement of Gene Expression Profiles in Toxicity Determinations" (April 17, 1997)

h) Acacia Biosciences Press Release (August 11, 1997)

i) Glaser, "Strategies for Target Validation Streamline Evaluation of Leads," Genetic Engineering News (Sept. 15, 1997)

APPENDIX - CLAIMS ON APPEAL

2. An isolated polynucleotide comprising a nucleic acid sequence encoding a protein having the amino acid sequence of SEQ ID NO:19 or the complete complement of the polynucleotide.

3. A composition comprising the polynucleotide of claim 2 and a reporter molecule.

4. An isolated polynucleotide consisting of the nucleic acid sequence of SEQ ID NO:68 or the complete complement of the polynucleotide.

5. A vector containing the polynucleotide of claim 2.

6. A host cell containing the vector of claim 5.

7. A method for using a polynucleotide to produce a protein comprising:

a) culturing the host cell of claim 6 under conditions for the expression of the protein; and

b) recovering the protein from the host cell culture.

8. A method for using a polynucleotide to detect expression of a nucleic acid in a sample, the method comprising:

a) hybridizing the polynucleotide of claim 2 to nucleic acids of the sample, thereby forming a hybridization complex; and

b) detecting hybridization complex formation, wherein complex formation indicates the expression of the polynucleotide in the sample.

9. The method of claim 8 wherein the polynucleotide is attached to a substrate or bonded to the surface of a microarray.

10. The method of claim 8 wherein the nucleic acids of the sample are amplified prior to hybridization.

11. A method of using a polynucleotide to screen a plurality of molecules to identify a ligand, the method comprising:

a) combining the polynucleotide of claim 2 with a plurality of molecules under conditions to allow specific binding; and

b) detecting specific binding, thereby identifying a ligand which specifically binds the polynucleotide.

12. The method of claim 11 wherein the molecules are selected from DNA molecules, RNA molecules, peptide nucleic acids, artificial chromosome constructions, peptides, and transcription factors.

13. A method for diagnosing a disease associated with gene expression in a sample containing nucleic acids, the method comprising:

a) hybridizing a polynucleotide of claim 2 to nucleic acids of the sample under conditions to form a hybridization complex,

b) comparing hybridization complex formation with standards, thereby diagnosing the disease.

14. The method of claim 13 wherein expression is diagnostic of lung cancer.

21. The method of claim 13 wherein the sample is from lung.